Fischetti '299 patent as disclosing that the chelating agents are included in such a way as to synergistically enhance the other components in the formulation. The Examiner has indicated that the Fischetti '299 patent "though disclosing the synergistic relationship of the chelating agents to the remains in formulation is silent to the specific concentration" and discloses a different buffering agent.

The Examiner has cited the Viegas '443 patent as disclosing a topical wound healing composition comprising chelators such as EDTA (citing Column 11, lines 18-20), antimicrobial agents such as tetracycline and amikacin (citing Column 10, lines 20-22), along with buffers such as phosphate and tromethamine (TRIS) which maintain the pH of the formulation at 7.4 (citing Column 11, lines 35-55). The Examiner indicated that drugs are present in a concentration of the Viegas '443 patent in amounts from 0.1-60% (citing Column 11, lines 28-31), while the buffer is present in a concentration of as much as 5%, which is sufficient to maintain the pH at 7.4 (citing Column 11, lines 50-60), and that the formulation can be applied to wounds as a second skin that delivers active agents to the affected site (citing Column 5, lines 1-5). The Examiner indicated that it would have been obvious to include the buffer agents of the '446 patent [*sic*, the Viegas '443 patent] into the formulation of the '299 patent since they both describe topical wound healing formulations comprising similar chelators, antimicrobial agents, and buffering agents.

Finally, the Examiner has concluded that it would have been obvious to follow the suggestions and teachings of the prior art in order to provide an improved method of treating bacterial infections, that the artisan of ordinary skill would have been motivated to combine the chelating concentration of the '979 patent [*sic*, the Viegas '443 patent] into the treatment method of the '299 patent in order to maintain the synergistic properties of the components and improve the treatment of the infection, and that one of ordinary skill in the art upon combining these

teachings, suggestions, and disclosures would have expected a treatment method suitable for the disinfecting surface injuries.

This rejection is respectfully traversed.

The Fischetti '299 patent primarily discloses an aerosol composition for treating *Streptococcus pneumoniae, Haemophilus influenzae* or Streptococcus Group A infections of the respiratory tract by delivering the aerosol to the mouth, throat or nasal passage, although passing is made of other organisms against which lytic enzymes can be targeted and other delivery routes. The active component of the composition of the Fischetti '299 patent is a lytic enzyme genetically coded by a bacteriophage specific for the specific bacteria of the respiratory tract (or other location) to be treated. The invention of the Fischetti '299 patent is based upon the discovery that phage lytic enzymes specific for bacteria infected with a specific phage can break down the cell wall of the bacterium in question. At the same time, the semipurified enzyme is lacking in proteolytic enzymatic activity and therefore non-destructive to mammalian proteins and tissues when present during the digestion of the bacterial cell wall (Column 3, lines 6-12). The Examiner's reference to the Fischetti '299 patent disclosing "the synergistic relationship of the chelating agents to the remains in formulation" apparently is based on Column 11, lines 16-32, which states:

> In order to accelerate treatment of the infection, the therapeutic agent may further include at least one complementary agent which can also potentiate the bactericidal activity of the lytic enzyme. The complementary agent can be penicillin, synthetic penicillins bacitracin, methicillin, cephalosporin, polymyxin, cefaclor. Cefadroxil, cefamandole nafate, cefazolin, cefixime, cefinetazole, cefonioid, cefoperazone, ceforanide, cefotanme, cefotaxime, cefotetan, cefoxitin, cefpodoxime proxetil, ceftazidime, ceftizoxime, ceftriaxone, cefriaxone moxalactam, cefuroxime, cephalexin, cephalosporin C, cephalosporin C sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephradine, cefuroximeaxetil, dihydratecephalothin, moxalactam, loracarbef mafate, chelating agents and any combinations thereof in amounts which are effective to synergistically enhance the therapeutic effect of the lytic enzyme.

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However, the role of chelating reagents in the enzyme compositions is explained elsewhere in the Fischetti '299 patent. The lytic enzymes of the Fischetti '299 patent are placed in a stabilizing buffer for maintaining the pH of the enzyme composition in a range of about 4.0 to about 9.0. The stabilizing buffer may be a reducing reagent, such as dithiothreitol, a metal chelating reagent, such as ethylenediaminetetraacetic acid disodium salt, or it may contain a phosphate or citrate-phosphate buffer. (See the Fischetti '299 patent, Column 5, lines 1-12, Column 6, lines 43-53, and Column 7, lines 53-64.) Thus, amounts of a chelating agent effective to "synergistically enhance the therapeutic effect of the lytic enzyme" as disclosed by the Fischetti '299 patent appear to be amounts (undisclosed) effective to maintain the pH of the composition in the range of about 4.0 to about 9.0 to stabilize the enzymatic activity of the lytic enzyme. The Fischetti '299 patent contains no disclosure or suggestion of inhibiting proliferation of a bacterial population of a skin injury or surface lesion of a patient by contacting the surface of the skin injury or the surface lesion with an antibacterial composition consisting of from 0.04 wt % to 25 wt % of a pharmaceutically acceptable antibacterial agent, from 0.1 mM to 100.0 mM a pharmaceutically acceptable chelating agent selected from EDTA, TRIEN and diethyltriamin-pentaacetic acid (DPTA), and an amount of tris (hydroxymethyl) aminomethane effective to maintain the pH of the composition in the range of 7.0 to 9.0 when in contact with the skin injury or surface lesion, wherein the antibacterial agent is present in the composition at a concentration selected to allow synergistic cooperation between the antibacterial agent and the chelating agent, as required by the claims of the present application.

The Viegas '443 patent discloses polymer gel formulations for the delivery of drugs or diagnostic agents to the cornea of an eye for use, for example, in connection with laser keratectomy or excimer laser surgery. The formulations of the Viegas '443 patent comprise an aqueous mixture of a film forming, water soluble polymer and an ionic polysaccharide. The

invention of the Viegas '443 patent is based on the discovery that, ". . . aqueous pharmaceutical vehicles containing a film forming polymer and an ionic polysaccharide can be gelled and rendered resistant to shear thinning by contacting the mixture with a counter-ion." (See the Viegas '443 patent, Column 6, lines 9-13.) Especially preferred counter-ion containing inorganic salts for use as ionic polysaccharide gelling agents include inorganic salts, such as calcium chloride, and are provided in a molar ratio of counter-ion to gellan, chitosan or alginate of about 1:1 to about 10:1 (see the Viegas '443 patent, Column 8, lines 34-41). As disclosed in the Viegas '443 patent at Column 10, lines 7-10:

> The gel compositions formed upon contact with a counter ion for the ionic polysaccharide allow retention of the gel at the desired locus for longer intervals thus increasing the efficiency of action of the delivered drug. . . .

The single appearance of the term "chelating agent" or EDTA in the specification of the Viegas '443 patent occurs at Column 11, lines 19 and 20, as part of a laundry list of "other drugs" that can be used in the treatment of conditions and lesions of the eyes. However, any EDTA that might potentially be present in a formulation of the Viegas '443 patent would inherently be present for an entirely different purpose than in the antibacterial compositions of the present invention. As disclosed in the present application at page 5, lines 3-7, EDTA is a strong chelating agent that removes divalent cations from the bacterial cell, altering the integrity and permeability of the outer membrane. In accordance with the present claims, the chelating agent and the antibacterial agent are present in the compositions of the claimed methods at a concentration selected to allow synergistic cooperation between said antibacterial agent and said chelating agent to inhibit proliferation of the bacterial population. However, the compositions of the Viegas '443 patent require the presence of high concentrations of a counter ion that would form a counter ion-EDTA coordination complex chelate with any EDTA present thereby blocking any further chelating function by the EDTA in the composition. Accordingly, the

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compositions disclosed in the Viegas '443 patent would be inoperable for use in the invention claimed in the present application and teach directly away from the compositions required in the methods of the present claims.

It is readily apparent from the foregoing that the Viegas '443 patent does not overcome the deficiencies of the Fischetti '299 patent and that, even when combined, one of ordinary skill in the art could not arrive at the present invention.

In view of the foregoing comments, it is respectfully submitted that Claims 1, 2, 5-8, 10-15, 18, 21, 22 and 56-62 would not have been obvious under 35 U.S.C. 103(a) over the combined disclosures of the Fischetti '299 patent in view of the Viegas '443 patent, and that this rejection of claims should properly be withdrawn.

Rejection of Claims 1, 2, 5-15, 18-22 and 56-62 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1, 2, 5-15, 18-22 and 56-62 under 35 U.S.C. § 103(a) as being unpatentable over the combined disclosures of the Fischetti '299 patent and the Viegas '443 patent, as discussed above, in view of Cuny et al. (U.S. Patent No. 6,207,679 hereafter the Cuny '679 patent). The Examiner has characterized the rejected claims as being drawn to a method of treating specific injuries and has cited the Cuny '679 patent as teaching the use of antimicrobial agents in the treatment of infections (bacterial/fungal) in wounds such as burns, ulcers, scrapes and bruises (citing the abstract, and Column 34, lines 40-55). The formulation comprises various antimicrobial agents such as penicillins, amino glycosides, and cephalosporins along with carriers and chelators such as EDTA (Column 36, lines 7-16; Column 38, lines 19-20). The Examiner concluded that the skilled artisan would have been motivated by these teachings to administer the formulation of the Fischetti '299 patent and the Viegas '443 patent combination to the skin for wound treatment as taught by the Cuny '679 patent. It is the Examiner's position that it would have been obvious to follow the suggestions of the Fischetti

'299 patent and the Viegas '443 patent combination in order to topically treat bacterial infections with an expected result of a method of treating infected wounds.

The deficiencies in the disclosures of the Fischetti '299 patent and the Viegas '443 patent are discussed in detail above and are fully applicable to this rejection.

As discussed in applicants' prior responses, the Cuny et al. '679 patent is directed to new antibacterial compounds--a specifically disclosed family of 2-(3-indolyl)-4-quinolino-carboxamide compounds and their substituted derivatives. Although the Cuny et al. '679 patent contains a generic disclosure of virtually all pharmaceutically acceptable routes of administration of the compounds and does indicate that wetting agents, emulsifiers and lubricants, coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants (including EDTA) can also be present in compositions of the new family of compounds, there is no disclosure or remote suggestion of topically administering a composition containing synergistic concentrations of a pharmaceutically acceptable antibacterial agent and a pharmaceutically acceptable chelating agent selected from EDTA, TRIEN and diethyltriamin-pentaacetic acid (DPTA), together with tris (hydroxymethyl) aminomethane (TRIZMA Base), and a pharmaceutically acceptable carrier, as required by applicants' amended claims. Accordingly, the Cuny et al. '679 patent does not overcome the deficiencies of the Fischetti '299 patent and the Viegas '443 patent, as discussed in detail above.

In view of the foregoing amendments and remarks, it is respectfully submitted that Claims 1, 2, 5-15, 18-22 and 56-62 would not have been obvious under 35 U.S.C. § 103(a) over the combined disclosures of the Fischetti '299 patent and the Viegas '443 patent in view of the Cuny '679 patent and that this rejection should properly be withdrawn.

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CONCLUSION

It is respectfully submit that Claims 1, 2, 5-15, 18-22 and 56-62 are in condition for allowance. Reconsideration and favorable action are requested. The Examiner is further requested to contact applicants' representative at the number set forth below to discuss any issues that may facilitate prosecution of this application.

Respectfully submitted,

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